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Health and Environmental Effects Profile for Terephthalic Acid

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TEREPHTHALIC ACID

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16. ABSTRACT

The Health and Environmental Effects Profile for Terephthalic Acid was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Terephthalic Acid.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

AFNOR	L'association Francaise de Normalisation (French)
BODT	Biological oxygen demand theoretical
CI	Confidence interval
DOC	Dissolved organic carbon
LD_{50}	Dose lethal to 50% of recipients
MITI	Ministry of International Trade and Industry (Japanese)
OECD	Organization for Economic Cooperation and Development
Development PEL	Permissible exposure limit
ppm	Parts per million
TLV	Threshold limit value
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Terephthalic acid is also known as p-benzenedicarboxylic acid; 1,4-benzenedicarboxylic acid; p-phthalic acid; TPA; benzene-p-dicarboxylic acid; and p-dicarboxybenzene (U.S. EPA/NIH, 1983). The structure of terephthalic acid is shown below:

Molecular formula: $C_6H_4(COOH)_2$

Molecular weight: 166.14

The Chemical Abstracts Service (CAS) Registry number for terephthalic acid is 100-21-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Terephthalic acid is a white crystalline solid at ambient temperature. Its high melting point makes it a difficult material to purify. Some of its physical and chemical properties are given below:

Melting point (sublimes):	>300°C (Bemis et al., 1982)
Density:	1.51 g/mℓ (Bemis et al., 1982)
Dissociation constants in aqueous solution at 25°C:	pK_1 = 3.54 (Bemis et al., 1982); pK_2 = 4.46 (Bemis et al, 1982)

Solubility:	1.9 mg/100 mL H_2O at 25°C, practically insoluble in ether, chloroform and acetic acid. Slightly soluble in cold alcohol, more soluble in hot alcohol. Soluble in alkalics (Windholz, 1983)
Vapor pressure:	9.75 mm Hg at 303°C (Bemis et al., 1982)

1.3. PRODUCTION DATA

Terephthalic acid is produced by the hydrolysis of dimethyl terephthalate or the oxidation of p-xylene (Bemis et al., 1982). SRI (1983) lists Hercofina, Wilmington, NC (240 million lbs/year), Standard Oil, Charleston, SC (1 billion lbs/year) and Decatur, Alabama (1.77 billion lbs/year), as producers of purified (fiber-grade) terephthalic acid. Tennessee Eastman and duPont produced an unstated amount of crude terephthalic acid for captive production of dimethyl terephthalate (SRI, 1983).

1.4. USE DATA

Polymer grade terephthalic acid is used extensively with dimethyl terephthalate (polymer grade) in the production of poly(ethylene terephthalate), which is the basic polymer used in fiber, film, and bottle-resin production (Bemis et al., 1982). The 1979 demand, by market shares, for terephthalic acid/dimethyl terephthalate are shown below:

	Market Shares %	
Market	U.S.	Worldwide
Polyester fiber	85	90
Polyester film	8	6
Polyester bottles	5	2
Other	2	2

Other applications of this compound are as intermediates in adhesives, coatings and various specialty chemicals. It is also used to produce saturated thermoplastics for application as engineering resins. Terephthalic acid has also been used to reduce the excretion rate of antibiotics in chickens (Giang et al., 1967).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Pertinent data regarding the atmospheric fate and transport of terephthalic acid were not located in the searched literature. Terephthalic acid aerosols and fumes could conceivably be released during shipping accidents and from molten production processes, but there are no reports of such incidences.

Several investigators have studied the degradation of terephthalic acid by soil microorganisms. Alexander and Lustigman (1966) reported the degradation of terephthalic acid by a suspension of Niagara silt loam as inoculum. Microbial degradation of terephthalic acid (20 µg/mℓ) as the sole carbon source was observed to occur when incubated in the dark at 25°C. A total loss of UV light absorption at terephthalic acid's characteristic wavelength (260 nm) occurred after 2 days of incubation.

Aftring et al. (1981) reported that bacteria isolated from Mississippi River sediment grew anaerobically and aerobically on terephthalic acid. After a 90-minute lag period, bacterial O_2 uptake was rapid. Anaerobic microbial respiration with no lag period was observed in the presence of nitrate.

Gerike and Fischer (1979, 1981) reported that terephthalic acid was readily degraded in a series of tests used by worldwide governmental agencies to assess the persistence of chemical compounds. They reported 93% DOC removal after 4 days in a Zahn Wellens test, 0% DOC removal and a 0% BODT after 14 days in a MITI test, 72% CO_2 evolution and 91% DOC removal after 42 days in a Sturm test, 82% DOC after 19 days in an OECD Screening Test, 112% of theoretical BOD in 30 days in a Closed Bottle Test, 66% DOC removal after 28 or 42 days and 0% inhibition after 7 days in the AFNOR test, and 93% DOC removal after 1 day in the Coupled Units Test. The

Coupled Units Test, Zahn Wellens test and MITI test may involve elimination mechanisms other than biodegradation and may represent phenomenon occurring in sewage treatment plants. The Sturm, OECD, AFNOR and Closed Bottle Test may, with simple precautions, be viewed as true biodegradability tests and may represent surface water models (Gerike and Fischer, 1979).

Engelhardt et al. (1976) reported that 3 of 7 bacteria isolated from soil grew on terephthalic acid as the sole carbon source. Three species of Nocardia completely degraded terephthalic acid (4 mg/mℓ, probably as the anion) to a total loss of UV light absorbance in 120 hours. Two species of Arthrobacter, one species of Alcaligenes and one species of Pseudomonas did not grow on terephthalic acid when provided as the sole carbon source. Keyser et al. (1976) observed the microbial degradation of terephthalic acid to protocatechuate via an unknown intermediate utilizing suspensions of Pseudomonas fluorescens, P. testosteroni EN 5a and a Pseudomonas EN_3. Kurane et al. (1977) observed that the bacterium Pseudomonas acidovorans degraded 3000 ppm terephthalic acid in 30 days in a shaking culture incubation at 30°C. Elmorsi and Hopper (1981) reported that a species of Pseudomonas grew on terephthalic acid and resulted in the ring fission of the compound. Another bacterium, tentatively identified as coryneform, did not grow on terephthalic acid.

The experiments reported by Anbar et al. (1966) provide data that can be used to calculate a half-life of terephthalic acid in water. The reaction rate constant of hydroxyl radicals with terephthalic acid was determined to be 1.92×10^9 M^{-1} sec^{-1}. Based on this rate constant value and a concentration of hydroxyl radicals of 10^{-17} M in aquatic media (Mill et al., 1980), the half-life of terephthalic acid in aquatic media due to this reaction can be calculated to be 1.14 years.

3. EXPOSURE

Leenheer et al. (1976) studied the fate and reactions of the constituents (including terephthalic acid) of industrial waste after deep well injection. Analysis of the waste indicated that it contained an average terephthalic acid concentration of 459 mg/ℓ, which was equivalent to 255 mg/ℓ DOC, and represented 3.7% of the total DOC. Water wells were drilled 1400-2700 feet from the injection site, and samples were obtained 2-4 years after injection. Samples from three wells contained 6.8, 3.2 and 5.4 mg terephthalic acid/ℓ.

Matsumoto (1982) gathered samples from industrially-polluted Tokyo rivers and measured 1.1-3.4 µg/ℓ (average 1.3±0.85-90% CI) of terephthalic acid. Water samples obtained from remote (unpolluted) rivers contained no detectable terephthalic acid.

4. PHARMACOKINETICS

4.1. ABSORPTION

Terephthalic acid has been observed to be rapidly absorbed when administered orally (Wolkowski-Tyl et al., 1982a; Moffitt et al., 1975; Hoshi and Kuretani, 1967) or by intratracheal instillation (Moffitt et al., 1975), but not when applied to skin (Moffitt et al., 1975). Absorption of terephthalic acid after oral administration, however, is not complete (Chin et al., 1981).

Hoshi and Kuretani (1967) characterized the gastrointestinal absorption of [^{14}C-carboxyl]-terephthalic acid in female Wistar rats given a single gavage dose of 85 mg/kg. The compound was administered to groups of five rats as a suspension in a 0.5% sodium carboxymethylcellulose. The esophagus, stomach, small intestine, caecum and large intestine of rats were assayed for radioactivity 2, 4, 6, 8, 24 and 48 hours after administration. Urine and feces were collected from treated rats after 8, 24 and 48 hours, and assayed for radio-activity. Expired CO_2 was collected for 24 hours and assayed for radioactivity. Expired air and feces collected for 24 hours accounted for <0.04 and 3.3% of the total radioactivity administered, respectively. The dose was absorbed rapidly, as it was excreted in the urine almost quantitatively by 48 hours. After examining the various gastrointestinal segments, the authors calculated that ~70 and ~26% of the administered dose was absorbed from the upper (i.e., stomach and small intestine) and lower (i.e., caecum and large intestine) portions, respectively.

Hoshi et al. (1966) observed the absorption and disappearance of terephthalic acid in the plasma of rabbits and rats given the compound orally and by i.p. injection. Plasma levels of terephthalic acid in the rabbit reached maximum values within 1 hour after injection, decreased gradually and were

not detectable after 24 hours. The half-life for elimination was reported to be ~1.8 hours. After oral administration of 100 or 200 mg/kg to the rabbit, the maximum plasma concentration was reached in 8-10 hours, and diminished with a half-life of 27 hours. In rats, the plasma half-life of terephthalic acid was ~1 and 3.4 hours for i.p. and oral administration, respectively.

Wolkowksi-Tyl et al. (1982a) studied the absorption of ^{14}C-terephthalic acid when administered to F344 rats by gavage. A single dose of the radiolabeled compound was suspended in aqueous 0.5% sodium carboxymethylcellulose and given by gavage to rats fasted for 12 hours. Radioactivity appeared in the plasma of treated rats in <25 minutes, and declined slowly for up to 400 minutes after dosing.

Moffitt et al. (1975), on the basis of excretion studies, concluded that terephthalic acid was rapidly absorbed regardless of the dose by the oral and inhalation routes in rats upon single or repeated administration. Negligible absorption was observed when the compound was dermally administered in single or repeated doses. At least 32% of the radioactivity contained in a single dose of uniformly ring-labeled ^{14}C-terephthalic acid was excreted in the urine of CR rats within 24 hours and >37% was excreted in the urine by 48 hours after administration by gavage. These results were obtained over a range of dose levels from trace amounts through 40 mg; similar results were obtained with repeated oral administration (5 doses during 10 days). Experimental details are provided in Section 4.4. In similar studies by Moffitt et al. (1975), rats were given ^{14}C-terephthalic acid by dermal application or intratracheal administration. Absorption by the dermal route was less efficient than by the oral route. Less than 5% of the total single or repeated dermal dose of radioactivity was excreted in

the urine and ~2% was excreted in the feces during the 10 days the compound was in contact with the skin. In the intratracheal experiments, 57% of the dose was excreted in the urine within 24 hours and 67% was excreted in the urine within 48 hours of administration of a single dose. An additional 6% was excreted in the feces within 48 hours. About 83 and 9% of the dose given by repeated intratracheal administration (5 doses during 10 days) was found after 24 hours in the urine and feces, respectively. Experimental details are provided in Section 4.4. It should be noted that the vehicle for the oral studies was peanut oil, whereas the vehicle for the dermal and intratracheal studies was 1% Triton X-100 in distilled water.

4.2. DISTRIBUTION

Hoshi and Kuretani (1968) studied the distribution of [^{14}C-carboxyl]-terephthalic acid in the female Wistar rat. Groups of five animals were given a single gavage dose of 85 mg terephthalic acid suspended in 0.5% sodium carboxymethylcellulose. Animals were killed and their blood and tissues assayed for radioactivity 2, 4, 6, 8, 24 and 48 hours after administration. Samples of plasma, kidney, liver, brain, skin, lung, pancreas, spleen, fat, heart, muscle, bone, erythrocytes, uterus, ovary and endocrine glands contained terephthalic acid up to 6 hours after administration, with the kidney having the highest concentrations, followed by the liver and plasma. No radioactivity was observed in any of the above tissues 48 hours after administration. The biological half-life of terephthalic acid in these tissues was 1.2-3.3 hours, and elimination followed first-order kinetics. Similar results were observed in rats fed a diet containing 0.5% [^{14}C-carboxyl]-terephthalic acid for 1 or 3 days, and killed immediately or 1 day after exposure. These results showed that terephthalic acid was widely distributed in various body tissues, but did not accumulate in any of them.

Moffitt et al. (1975) gave male CR rats repeated (every other day for 5 doses in 10 days) doses of uniformly ring-labeled ^{14}C-terephthalic acid by gavage as described in Section 4.4., and assayed their organs for radioactivity on day 10, 24 hours after administration of the last dose. The radioactivity found in the blood, liver, lung, heart, kidney, spleen, adrenals, pancreas, testes and brain accounted for <0.1% of the total dose, regardless of its amount. Repeated administration of the compound by intratracheal instillation and dermal application gave similar results. In addition, with intratracheal administration, <1% of the dose of radioactivity was found in the lungs and tracheal lymph nodes. The compound apparently is not retained in the tissues of rats under these experimental conditions.

Wolkowski-Tyl et al. (1982a) studied the distribution of ^{14}C-terephthalic acid in F344 rats after gavage administration and i.v. injection. Unanesthetized rats were given a bolus i.v. injection of ^{14}C-terephthalic acid in an aqueous buffer solution. Blood samples were drawn from jugular vein cannulas, and were assayed for radioactivity at selected intervals up to 400 minutes after injection. The data were found to best fit a 3-compartment model, with an average terminal half-life of 1.2 hours, and average volumes of distribution of 107.3 and 1312.7 mℓ/kg for plasma and all compartments, respectively. When rats were given the compound by gavage (as a 0.5% aqueous sodium carboxymethylcellulose solution), the data regarding plasma concentrations with time were best fit with a 2-compartment model with first order absorption. A longer terminal half-life was observed with oral administration than with i.v. injection, indicating that absorption or dissolution of terephthalic acid from the gut may be partially rate limiting.

Wolkowski-Tyl et al. (1982a) also characterized the distribution of terephthalic acid in pregnant F344 rats. Terephthalic acid was observed to cross the placenta and was present in fetal bladders. The amount of terephthalic acid available to the fetus was sufficient to cause neonatal bladder stones at maternal dietary levels of 5% but not 0.5% (see Section 5.4. for experimental details).

4.3. METABOLISM

Terephthalic acid is apparently rapidly absorbed and excreted unchanged in the urine (Wolkowski-Tyl et al., 1982a; Hoshi and Kuretani, 1965, 1968; Moffitt et al., 1975) and feces (Moffitt et al., 1975) of rats upon oral administration. Hoshi and Kuretani (1967) attempted to identify the urinary metabolites of [^{14}C-carboxy]-terephthalic acid after feeding rats a diet containing 0.5% of the compound. Urine fractions collected between 4 and 6 hours after feeding rats the test diet were analyzed by thin layer chromatography. Autoradiography revealed a single radioactive spot corresponding to intact terephthalic acid; no metabolites corresponding to phenolic compounds, glucuronic acid or glucuronolactone conjugates were observed.

Wolkowski-Tyl et al. (1982a) found no evidence of ^{14}C-terephthalic acid metabolism in rats given an i.v. dose of the compound. Gradient High Pressure Liquid Chromatography of urine collected from treated animals showed a single, sharp radioactive peak that corresponded to terephthalic acid.

4.4. EXCRETION

Hoshi and Kuretani (1965) studied the excretion of terephthalic acid when given to rats by gavage, i.p. injection and dietary inclusion. When a gavage dose of 200 mg/kg suspended in 0.5% aqueous sodium carboxymethylcellulose was given to rats, terephthalic acid was found 24 hours after

administration in the urine and feces, and accounted for ~55 and 30% of the dose, respectively. When a similar dose was given by i.p. injection, most of the dose was recovered quantitatively in the urine after 24 hours. When fed 300 mg terephthalic acid/kg/day, rats excreted 78-85% of the dose in urine and the rest in feces by 24 hours after feeding. No other experimental details were found in the available abstract (Hoshi and Kuretani, 1965).

Hoshi and Kuretani (1967) monitored the expired air, urine and feces of rats given a single gavage dose of 85 mg [^{14}C-carboxyl]-terephthalic acid suspended in 0.5% aqueous carboxymethylcellulose. Twenty-four hours after administration, the urine, feces and expired air accounted for 93.5, 3.3 and <0.04% of the radioactivity administered, respectively. After 48 hours, the integrated excretion of radioactivity in the urine and feces was 93.8 and 3.3%, respectively.

Moffitt et al. (1975) studied the excretion of uniformly ring-labeled ^{14}C-terephthalic acid following single and repeated oral, intratracheal and dermal administration to male Charles River rats. In the oral experiment, groups of five rats received single or repeated (5 doses over 10 days, alternate days) doses of 4 ,Ci ^{14}C-terephthalic acid (specific activity not reported) along with 0, 40 or 80 mg of unlabeled terephthalic acid in peanut oil by gavage. The urine and feces were collected, and the repeated-dose animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). In the single-dose experiments, >80% of the administered radioactivity was excreted in the urine and feces within 48 hours of administration; the excreted radioactivity appeared to be evenly distributed between the feces and urine. In the repeated-dose experiments, >89% of the administered radioactivity was found

in the urine and feces within 24 hours of the last administration; about half of this excreted radioactivity was found in the urine. A linear correlation between urinary and fecal excretion with time and dosage was observed with repeated administration.

In the intratracheal experiment, groups of five rats received single or repeated (5 doses over 10 days, alternate days) doses of 6 μCi ^{14}C-terephthalic acid (specific activity not reported) along with 0, 5 or 10 mg unlabeled compound in aqueous Triton X-100 emulsions by intratracheal injection (Moffitt et al., 1975). The urine and feces were collected, and the repeated-dose animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). Approximately 49-73% of the single intratracheal dose was recovered mostly in the urine (46-67%), with smaller quantities in the feces (3-6%) 48 hours after dosing. Similar results were obtained with repeated intratracheal administration.

In the dermal experiment, groups of five rats received single or repeated (5 doses over 10 days, alternate days) doses of 80 mg of uniformly ring-labeled ^{14}C-terephthalic acid (4 μCi) in aqueous Triton X-100 emulsions to their shaved backs (Moffitt et al., 1975). In both the single dose and repeated dose studies, a gauze patch was used to cover the dose area (1 inch^2) for 10 days, and was removed only to allow repeated dosing. The urine and feces were collected during the entire 10 days, and the animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). Approximately 41, 19 and 26% of the recovered radioactivity was found in the urine, feces and application area, respectively.

Wolkowksi-Tyl et al. (1982a) studied the urinary excretion of a bolus i.v. dose of ^{14}C-terephthalic acid in F344 rats. Rats were anaesthetized with sodium barbital and given an intravenous dose of the compound via a tail vein. Urine samples were collected at 30-minute intervals by bladder puncture, and assayed for radioactivity. Rapid excretion of radioactivity occurred, with 101$\pm$8% of the injected dose recovered in the urine after 8 hours. The data best fit a two phase excretion model. When unanesthetized rats were given the compound by jugular i.v. injection, the plasma clearance rate was very similar to the glomerular filtration rate of the rat, suggesting that terephthalic acid is primarily excreted by the kidney.

5. EFFECTS

5.1. CARCINOGENICITY

Gross (1974) reported that terephthalic acid induced the formation of bladder and ureteral neoplasms in male and female Wag/Rij (Wistar) rats maintained on diets containing 5% terephthalic acid. No tumors were observed in rats maintained on diets containing <1% terephthalic acid. This information was obtained from Chin et al. (1981), and further details of tne experiment can be provided when the original study is located.

No other data are available to support the carcinogenicity of terephthalic acid. Heck and Kluwe (1980) demonstrated that dimethyl terephthalate is readily metabolized to terephthalic acid and excreted in the urine. It is of interest to note that an NCI (1979) bioassay of dimethyl terephthalate reported no increased tumor incidence in rats and mice maintained on diets containing up to 5000 ppm dimethyl terephthalate for 103 weeks.

Nagasawa and Fujimoto (1973) demonstrated that chronic feeding of low levels of terephthalic acid resulted in a significantly decreased incidence of spontaneous mammary tumors in mice. A group of 31 female C3H/He mice (aged 23-25 days) was maintained on a diet containing 0.5% terephthalic acid for 16 months. A control group of 116 females received a commercial diet for 16 months. Administration of terephthalic acid for $\geq$6 months was observed to significantly decrease the cumulative percentage of mice with mammary tumors. The authors suggested that terephthalic acid may play an important role in the maintenance of homeostasis.

5.2. MUTAGENICITY

Florin et al. (1980) reported the absence of mutation in Salmonella typhimurium with terephthalic acid in Ames assays. S. typhimurium strains TA98, TA100, TA1535 and TA1537 treated with 3 µmole terephthalic acid/

plate did not mutate in the presence or absence of rat liver S-9. Terephthalic acid has been reported to be nonreactive as an electrophile (Bezuglyi and Novick, 1960).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of terephthalic acid were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Nagasawa and Fujimoto (1973) fed 116 and 31 female C3H/He mice diets containing 0 and 0.5% terephthalic acid for 47-55 days prior to mating with untreated males. No differences between control and treated groups were observed with respect to litter size, average weights and rate of weight gain of pups or incidence of tumors in pups.

Ledoux et al. (1982) reported fetotoxic effects in the offspring of Wistar and CD rats maintained for 90 days on diets containing terephthalic acid prior to mating. Both males and females were fed diets containing 0, 0.03, 0.125, 0.5, 2.0 or 5.0% terephthalic acid for 90 days. Ten breeding pairs of each strain were then established for each dietary level. These pairs were continued on their respective diets throughout mating, gestation, lactation and weaning. No effect on fertility index or litter size was observed for either strain at any dose level. Adverse effects in the fetuses and neonates, however, were observed at the maternal dietary levels of 2 and 5% terephthalic acid. Reductions in viable offspring at birth, day 1 (Wistar male pups) and survivability to day 21 (CD female pups at 5% level) were observed. The following body weights were found to be significantly lower than the control group: day 1 Wistar pups at the 5% dietary level and day 21 Wistar and CD pups at the 5% dietary level.

Wolkowski-Tyl et al. (1982a) fed pregnant F344 rats diets containing 0.5 or 5% terephthalic acid starting on day 7 of gestation. An additional group of dams were given diets containing 0.5% terephthalic acid commencing on postnatal day 1. Dietary treatment of dams continued through lactation and pups were continued on the same diet through day 45 of age. An additional group received control diets throughout. An increased incidence of neonatal bladder stones in both male and female pups was observed in both groups given 5% terephthalic acid diets, but only after postnatal day 25 (i.e., only when the pups started ingesting the chemical directly in the diet). No neonatal bladder stones were observed in groups fed 0.5% terephthalic acid or control diets. Uniformly ring-labeled (^{14}C)-terephthalic acid was given to pregnant rats on day 20 of gestation to further characterize the placental transport and distribution of the compound in the fetus. At selected times from 45 minutes to 12 hours after administration, placentas, amniotic fluid and fetal serum, livers, kidneys and bladders were collected and assayed for radioactivity. The highest concentrations of radioactivity were found in fetal bladders 1.5 hours after administration. While terephthalic acid was observed to cross the placenta, it did so in insufficient quantities to cause urolithiosis. Direct feeding of diets containing a high concentration of terephthalic acid was required to cause this effect.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Rats maintained on a 3% terephthalic acid diet developed urinary-bladder calculi in 60 days and kidney calculi in 90 days (Amoco, 1979). Urolithiosis was also studied by Ledoux et al. (1982), but the results were not provided in the available secondary reference (U.S. EPA, 1982).

Gross (1974) reported that Wistar rats maintained on diets containing 5% terephthalic acid for 2 years developed a high incidence of bladder stones.

No toxic effects were observed in rats maintained on diets containing <1% terephthalic acid for 2 years. This information was obtained from Chin et al. (1981), and further experimental details can be provided when the original study is located.

5.6. OTHER RELEVANT INFORMATION

Short-term exposures to terephthalic acid have been reported to cause irritation (U.S. EPA-NIH, 1983) and induce the formation of bladder stones in rats. Administration of diets containing ≥3% terephthalic acid caused urolithiosis in rats after 2 weeks (Wolkowski-Tyl et al., 1982b; Chin et al., 1981). The composition of the stones was mostly terephthalic acid and calcium. Other effects observed to be associated with bladder stone induction include hyperplasia of the transitional epithelium of the bladder (Wolkowski-Tyl et al., 1982b) and aciduria and hypercalcuria (Chin et al., 1981). Dietary concentrations of <1.5% terephthalic acid were not observed to induce bladder stone formation (Chin et al., 1981). When fed to rats for 7 days, a diet containing 0.5% terephthalic acid did not affect kidney excretion of a marker dye, plasma transaminase activity or the sugar, protein, free amino acid and urea content in plasma (Hoshi et al., 1968).

Acute lethal toxicity in terms of LD_{50}s has been reported in mice by the oral and i.p. routes to be >5000 and 1430 mg/kg, respectively (Hoshi et al., 1968). An LD_{50} for oral administration in rats of 18,800 mg/kg has been reported by NIOSH (1983).

6. AQUATIC TOXICITY

Pertinent data regarding the toxic effects of terephthalic acid on aquatic organisms were not located in the available literature. Terephthalic acid has, however, been identified at levels as high as 3.4 and 5.3 µg/ℓ in river water from the Tokyo area and in night soil treatment plant effluen., respectively (Matsumoto, 1982).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

There is no specific PEL or TLV for terephthalic acid exposure in occupational settings (NIOSH/OSHA, 1980).

According to the Code of Federal Regulations (21 CFR 175.320), terephthalic acid may be used in food contact adhesives if the chloroform soluble portion of water extractives of coated film obtained with distilled water at 120°F for 24 hours does not exceed 0.5 mg/inch² of surface area.

Terephthalic acid can be used in condensation polymerized resins intended for contact with food if the following two conditions are met:

1) net chloroform extractables do not exceed 0.1 mg/inch² of surface area when the prescribed food simulation solvent is water or 8-50% alcohol.

2) total nonvolatile extractives do not exceed 0.1 mg/inch² surface area when heptane is used as the food simulation solvent (21 CFR 177/2420).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of terephthalic acid were not identified in the available literature.

8. RISK ASSESSMENT

In experimental animals, terephthalic acid appears to be rapidly absorbed upon oral or intratracheal administration, but not when applied to skin (Wolkowski-Tyl et al., 1982a; Moffitt et al., 1975; Hoshi and Kuretani, 1967). Terephthalic acid is eliminated largely by the urinary and fecal routes, and appears to be excreted intact (Wolkowski-Tyl et al., 1982a; Hoshi and Kuretani, 1965, 1968; Moffitt et al., 1975).

Data demonstrative of terephthalic acid's carcinogenicity are equivocal. While Gross (1974) reported a tumorigenic effect in rats maintained on diets containing 5% of the compound, the unavailability of this document and the absence of corroborating evidence prevent the accurate assessment of terephthalic acid's carcinogenic potential at this time.

Terephthalic acid is known to be a metabolic product of dimethyl terephthalate, and is excreted mainly in the urine (Heck and Kluwe, 1980). Dimethyl terephthalate did not induce cancer in rats or mice maintained for life on diets containing up to 5000 ppm dimethyl terephthalate (NCI, 1979).

Terephthalic acid has been reported to give a negative response in Ames-type mutagenicity assays (Florin et al., 1980), and it does not have electrophilic reactivity (Bezuglyi and Novick, 1960).

The ability of terephthalic acid to produce bladder stones and bladder hyperplasia in rats after short-term administration has been demonstrated (Wolkowski-Tyl et al., 1982b; Chin et al., 1981). Aciduria and hypercalcuria have been associated with the development of bladder stones in rats maintained for 2 weeks on diets containing 0.5-4% terephthalic acid. These effects are consistent with the observed urinary excretion pattern of this compound.

Similar induction of bladder stones in rats has been reported after 90-day administration of terephthalic acid at 3% in the diet (Amoco, 1979) or 2-year administration of terephthalic acid at 5% in the diet (Gross, 1974). Decreased neonatal survival was observed in the offspring of pairs of male and female rats fed 2 or 5% terephthalic acid in their diets for 90 days prior to mating and then throughout gestation and lactation (Ledoux et al., 1982). The lack of experimental detail and the unavailability of these documents, however, precludes their use in risk assessment at this time.

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APPENDIX

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

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